The Dependence of BOLD fMRI and Somatosensory Evoked Potentials on Stimulation of the Rat Forepaw with Various Pulse Waveforms

A. G. Goloshevsky[1], A. C. Silva[1], S. J. Dodd[1], A. P. Koretsky[1]

[1]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, United States

Introduction: The anesthetized rat model of somatosensory stimulation has been very useful for studying various aspects of neurovascular coupling [1,2,3]. Mechanical stimulation of the whisker pad [1] or electrical stimulation of the paw [2,3] have provided extensive insights into the relation between neuronal activity and functional hyperemia, which underlie the contrast in fMRI, PET and optical imaging of intrinsic signals. In the model of electrical stimulation of the paw, the frequency and amplitude of short square stimulation pulses, as well as the duration of a train of pulses, have been varied [2,3]. A linear coupling between increases in neuronal activity, as measured by recordings of somatosensory evoked potentials (SEPs), and increases in cerebral blood flow (CBF) have been reported [3]. In this work, we investigated the effects of different stimulation pulse waveforms on neuronal activity, as measured by SEPs, and on the amplitude of the BOLD fMRI signal in rat somatosensory cortex. Each individual pulse waveform was characterized by its frequency content. The results indicated that stimulation pulses with power at lower frequencies elicited decreased SEPs and fMRI responses, compared to pulses with power at higher frequencies, which elicited larger SEPs and fMRI responses.

Materials and Methods: Sprague-Dawley rats were anesthetized with isoflurane and orally intubated. Arterial and venous catheters were inserted for sampling of blood gases and injection of drugs. Needle electrodes were inserted into a forepaw. The animals were placed on a stereotaxic head holder with ear and bite bars. To record SEPs, the rat skull was exposed and 700 μm burr-holes were drilled at 3.5 mm on both sides lateral to the bregma for the signal electrodes. One additional burr-hole 10 mm caudal to the bregma was drilled for the ground electrode. The electrodes were gently inserted until the dura was touched. Expired CO_2, rectal temperature and blood pressure were continuously monitored; blood gases were measured and maintained at normal levels. Anesthesia was switched to a continuous αchloralose infusion. A forepaw was stimulated by application of trains of pulses of current at a repetition rate corresponding to a frequency of 3 Hz. Waveforms of the pulses were varied and consisted of rectangular pulses of 333 μs duration, triangular pulses of different base-widths (Fig. 1) and sinusoidally-shaped pulses of 111 ms duration but at different frequencies (9, 18, 27, 45, 90, 180 Hz). Maximum current amplitude was 2 mA in all stimulations. Voltage waveforms were created and output using a MP150 Biopac system (Biopac Systems, Inc, Goleta, CA). An A395 linear stimulus isolator (World Precision Instruments, Sarasota, FL) was used for voltage-to-current conversion/isolation. SEPs were recorded using the MP150 Biopac system (differential input, gain of 5000). To obtain a mean SEP for each different stimulus waveform, averaging of the SEP responses over a 45 s long train of pulses was done. Functional MRI experiments were performed on an 11.7 T/31 cm magnet (Magnex Scientific, Ltd., Abington, UK) interfaced to a Biospec-Avance console (Bruker-Biospin, Corp, Billerica, MA). A home-built receiving surface coil was used. A spin-echo EPI sequence was employed with the following parameters: FOV 1.92x1.92 cm^2, matrix = 64x64, in-plane resolution 300 μm, TE = 30 ms, TR = 1.5 s. Five 1.5 mm thick slices were acquired, covering the forebrain and middle brain. The stimulation paradigm was 60 images (90 s) during rest, 30 during stimulation (45 s), and 60 images (90 s) during rest.

Results and Discussion: All SEP studies (n=4 rats for each specific pulse type) showed a dependence of obtained signals on the shape of stimulation pulses. The peak-to-peak amplitude of the SEPs decreased (Fig. 2) as the power of the low frequency harmonics increased in the power spectra of pulse waveforms. Times to peak of the responses were longer for longer times to peak of the stimuli. BOLD fMRI studies (n=5 rats for each specific pulse type) demonstrated a similar trend. Stimuli with power at the lower frequencies led to decreased amplitudes of the BOLD responses in SI compared to stimuli with power at higher frequencies (Fig. 3). Therefore, for lower frequency stimuli a lesser degree of neuronal activity as measured by the peak-to-peak amplitude of SEPs, corresponded to decreased BOLD signals as compared to higher frequency stimuli that had large SEPs and BOLD signals.

References: [1] Devor A et al, Proc Natl Acad Sci USA 2005, 102(10): 3822-7; [2] Silva AC et al, J Cereb Blood Flow Metab. 1999, 19: 871-9; [3] Ureshi M et al, Neurosci. Res. 2004, 48: 147-53

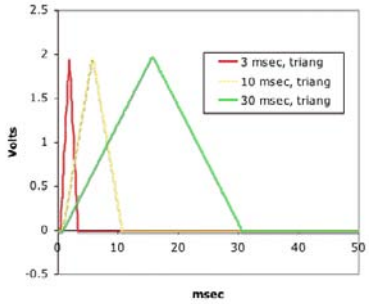

Figure 1: Triangular pulses of current with different base-widths were used for stimulation. Voltage waveforms are shown (1 V corresponded to 1 mA).

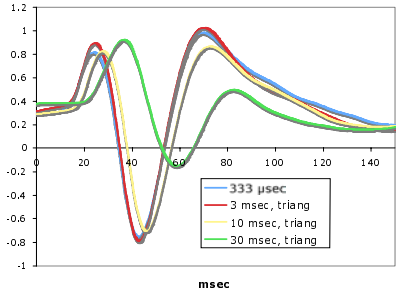

Figure 2: A forepaw was stimulated by application of the train of triangular pulses for 45 s. Frequency of pulses in the train was 3 Hz. SEPs for each pulse averaged over the train are shown. An SEP corresponding to 333 μs rectangular pulse is shown for comparison.

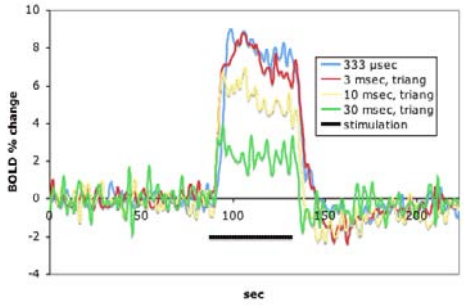

Figure 3: BOLD-fMRI time courses for the same stimuli.